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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,273	06/19/2003	Susan J. Braunhut	08688-057001 / UML 02-06	6439

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EXAMINER	
SCHUBERG, LAURA J	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,273	BRAUNHUT ET AL.	
	Examiner	Art Unit	
	Laura Schuberg	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-15 and 21-53* is/are pending in the application.

4a) Of the above claim(s) *11-15 and 21-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 47-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 11-15 and 21-53 are pending.

Claims 11-15 and 21-46 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species and inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/13/2006.

Claims 1-9 and 47-53 have been examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 47, 48, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rieck et al (Experimental Cell Research 1995) in view of Abraham et al (US 5,993,844).

Amended claim 1 is now drawn to a method of generating a morphogen composition from an extracellular matrix, the method comprising: growing cells on a surface under conditions and for a time sufficient to enable the cells to form an extracellular matrix (ECM); removing living cells from the surface using a non-proteolytic process and leaving the now substantially living cell-free ECM on the surface, wherein the cells remain intact upon removal; stimulating the substantially living cell-free ECM to release morphogens into the fluid; and collecting the fluid to form a morphogen composition. Dependent claims are drawn to wherein the morphogens are growth factors or differentiating factors (growth factors elected), wherein the morphogen composition comprises a plurality of morphogens, wherein the fluid comprises a biocompatible liquid or gel, the type of non-proteolytic process and the type of stimulation to the ECM (physical or chemical).

Rieck et al teach a method of extracting fibroblastic growth factor 2 (FGF2) from an ECM by growing endothelial cells, dissolving the cell layer with Triton X-100, exposing the subendothelial matrix, and extracting the FGF2 with either 2M NaCl or trypsin thus forming a morphogen composition with fibroblast growth factor and a biocompatible fluid (page 37-column 1 last paragraph- column 2). The NaCl is deemed to provide a chemical stimulus to extract the FGF2 and the trypsin is deemed to provide a physical strain to the ECM by hydrolysis of peptide bonds

Rieck et al do not teach wherein the cells remain intact upon removal.

Abraham et al teach an alternate method of forming an acellular collagenous matrix by first contacting tissue with an effective amount of chelating agent (column 6

lines 66-67) and washing with a buffer (column 7 lines 64-67). The chelating agents are taught to include EDTA and EGTA (column 7 lines 6-9) and the buffer is most preferably sodium chloride phosphate buffered saline (which lacks calcium and magnesium) (column 8 lines 19-25). The method is taught to overcome the difficulties in obtaining tissue matrices that are substantially collagen (column 3 lines 19-21).

Therefore, it would have been obvious for one of ordinary skill in the art to modify the method of Rieck et al to substitute the step of cell removal using detergent treatment (Triton X-100) with cell removal using chelating agents because Abraham et al teach that these methods are art recognized equivalents for cell removal while leaving the extracellular matrix substantially intact (column 3 lines 15-34). Also, the Abraham et al method would also have the added benefit of allowing the practitioner of subculturing the intact cells for further use, which the dissolving method with detergent (Triton X-100) would not allow. One of ordinary skill in the art would have had a reasonable expectation of success because both Rieck et al (page 37) and Abraham et al (column 3 line 64- column 4 line 3) were concerned with the selective preservation of the matrix after cell removal.

Therefore, the combined teachings of Rieck et al and Abraham et al render obvious Applicant's invention as claimed.

Claims 6-9, 49, 50, 51 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rieck et al (Experimental Cell Research 1995) and Abraham et al

(US 5,993,844) as applied to claims 1-5, 47, 48, 51 and 52 above, and further in view of Koyama et al (Nature Biotechnology 1997) and Simpson et al (US 2002/0090725 A1).

Amended claim 6 is now drawn to a method of generating a morphogen composition from an extracellular matrix comprising: growing cells on a surface under conditions and for a time sufficient to enable the cells to form an extracellular matrix (ECM); removing living cells from the surface using a non-proteolytic process and leaving the now substantially living cell-free ECM on the surface, wherein the cells remain intact upon removal; applying an electric potential to the substantially living cell-free ECM to release morphogens into the fluid; and collecting the fluid to form a morphogen composition.

Dependent claims further include wherein the electric potential cycles from negative voltage to a positive voltage and back to a negative voltage, wherein the electric potential ranges from –0.3 V to +0.3 V, varying frequency, potential range, potential cycle shape, or potential cycle number of the electric potential to control release and activation of specific morphogens, the type of non-proteolytic process, and wherein the electric potential has a power of less than 3.0 watts.

Rieck et al and Abraham et al combined teach a method of generating a morphogen composition from an extracellular matrix as described above.

Rieck et al do not teach wherein stimulating the ECM comprises applying an electric potential to the ECM.

Koyama et al teach that electrical stimulation markedly promoted the nerve growth factor (NGF) secretion from astroglial cells (page 165 column 1 lines 19-22).

Simpson et al teach that an electrical field can stimulate movement or conformational changes in a matrix due to the movement of magnetically or electrically sensitive particles. Such movement can affect the release of compounds from an electroprocessed matrix. Simpson et al also teach that electroprocessed material may be induced to release substances (such as growth factors) (page 27 para 223). Simpson et al further teach that altering the conformation of the matrix can increase or decrease the extent to which the material is favorable for compound release. Further, the porosity of the electroprocessed collagen can be regulated, which affects the release rate of the substance. Enhanced porosity facilitates release. Substance release is also enhanced by milling, fragmenting or pulverizing the electroprocessed collagen (applying a physical tension and strain to the ECM) (page 27 para 223).

Therefore, one of ordinary skill in the art would have been motivated to use an electric potential as an alternate method of stimulating the release of growth factors in the ECM in the method of Rieck et al because Koyama et al teaches that electrical stimulation promotes growth factor release from cultured cells (which include an ECM) and also because Rieck et al show that there is more than one way to extract growth factor from an extracellular matrix (page 37 column 2, line 6). Additional motivation and a reasonable expectation of success would have been provided by Simpson et al because they show that electrical stimulation of the matrix also affects release of compounds from the matrix (page 26 para 222 and page 28 para 230-231).

One of ordinary skill in the art would have been motivated to apply an additional physical tension or strain (such as milling or fragmenting) to the ECM in the method of

Rieck et al because Simpson et al teach that substance release is enhanced by milling, fragmenting or pulverizing electroprocessed collagen. One of ordinary skill in the art would have had a reasonable expectation of success because enhanced porosity facilitates release of substances from electroprocessed collagen.

The modulation of the electric potential to comprise varying power, frequency, potential range, potential cycle shape or potential cycle number would have been a matter of routine optimization for one of ordinary skill in the art. The artisan recognizing that the optimum electric potential power, frequency, cycle and voltage would produce a sufficient amount of cell growth and/or growth factor secretion with minimal power expended. One of ordinary skill in the art would have had a reasonable expectation of success because Simpson et al teach that an electrical field can stimulate movement or conformational changes in a matrix due to the movement of magnetically or electrically sensitive particles (page 28 para 230).

Therefore, the combined teachings of Rieck et al, Abraham et al, Koyama et al and Simpson et al render obvious Applicant's invention as claimed.

Response to Arguments

Applicant's arguments with respect to claims 1-9 have been considered but are moot in view of the new ground(s) of rejection. The arguments have been addressed in so far as they relate to the new rejections above.

Applicant argues that Koyama and Simpson are so different from the claimed invention that they cannot be combined with the method of Rieck and if combined would yield something quite different from the claimed invention.

This is not found persuasive because the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant argues that because Koyama's focus is using electric potential to induce cells to produce and secrete NGF, that one skilled in the art, at best, would have been motivated to apply a potential to living cells which would produce and secrete NGF. Applicant asserts that there would be no motivation to apply a potential to an ECM from which cells had been removed, because no cells were left to be induced to produce NGF.

This is not found persuasive because Koyama's teaching that an electric potential serves as a sufficient stimulus for the induction of NGF from cultured cells (which also include an extracellular matrix) is significant in that it shows that growth factors specifically respond to an electrical stimulus. Combined with the fact that we know that growth factors are present in the extracellular matrix (as taught by Rieck) and the teaching of Simpson that shows that electroprocessed collagen can be used to deliver substances one of ordinary skill in the art would find sufficient motivation to apply

an electric potential to the extracellular matrix of Rieck to induce release of growth factors. The combination of Koyama and Simpson demonstrate that an electric potential would serve as an alternate stimulus in the method of Rieck for extracting growth factors from an extracellular matrix.

Applicant argues that Simpson and Koyama have nothing to do with each other, and Simpson provides no incentive to release morphogens from ECM.

This is not found persuasive because Simpson and Koyama both discuss the value of using electric potentials to stimulate the release of desired compounds from biomaterial. Simpson provides a reasonable expectation of success that an ECM can be induced by an electric potential to release compounds, such as growth factors, that are present in the ECM (page 27 para 223).

Applicant argues that when used to deliver substances, Simpson's electroprocessed collagen releases substances by diffusion, by degrading over time, or by exposure to light and that there is no suggestion to stimulate release of any substances using electricity.

This is not found persuasive because Simpson specifically teaches using an electric field to move substances out of a collagen matrix (page 28 para 230-231).

Applicant argues that Simpson is limited with regard to using electric potential on a collagen matrix to release drugs that have been artificially introduced into the matrix along with electrically sensitive particles.

This is not found persuasive because Simpson merely uses the release of drugs as an example of a compound that can be moved from a collagen matrix. Growth

factors are also listed as potential compounds that can be released from an electrically processed collagen matrix (page 9 para 98). Electrically sensitive particles are cited as an example (page 28 para 230) and are not suggested as an additional requirement in order to allow release of a compound from a matrix.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is 571-272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Laura Schuberg